

## Cholesterol Emboli Syndrome: Significance of the Lesional Skin Biopsies

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Accepted February 21, 2005.

Sir,

Cholesterol emboli syndrome (CES) is an underdiagnosed multisystemic disease with important sequelae resulting in a poor prognosis with 80% mortality within 12 months after acquiring the disease. The syndrome usually affects elderly patients who have some known risk factors for vascular disease and is often precipitated by some trigger factor (1, 2). Diagnosis is based on suspicious clinical findings and can be confirmed by lesional tissue biopsy (1, 3). This article reports two cases of CES in relation to treatment with anti-coagulants. In both cases, diagnosis was established through biopsy of involved skin.

### CASE REPORTS

*Case 1.* A 73-year-old man with a long history of hypertension and chronic renal failure arising from nephrosclerosis (plasma creatinine 150  $\mu\text{mol/l}$ ) was admitted to our hospital with deteriorating renal function and bradyarrhythmia due to beta-blocker agents. The patient's medication at the time of the admission was nifedipine and enalapril. Two months prior to admission, he had been treated with warfarin and atenolol for management of paroxysmal atrial fibrillation.

Examination revealed a blood pressure of 120/70 mmHg and a pulse rate of 34. Bilateral livedo reticularis on his lower limbs was found with painful cyanotic ischaemic lesions of the right toes but intact peripheral pulses and good foot temperature. These lesions had been present for the past 45 days.

Blood chemistry was normal except for the following values: haemoglobin 1.52 mmol/l (normal 2.09–2.71), haematocrit 29% (41–53%), total white cell count  $11.5 \times 10^9/\text{l}$  ( $4.5\text{--}11 \times 10^9/\text{l}$ ) with eosinophils  $1.7 \times 10^9/\text{l}$  ( $0.05\text{--}0.25 \times 10^9/\text{l}$ ), plasma urea 62.4 mmol/l (2.5–6.4), plasma creatinine 583  $\mu\text{mol/l}$  (53–106), potassium 5.8 mmol/l (3.5–4.5), serum cholesterol 6.73 mmol/l (3.66–6.20) and ESR 80 mm/h (0–9). Urine analysis showed a 1+ test result for protein and red blood cells. Microscopy of a skin biopsy from a livedo reticularis area near the necrotic zone revealed the presence of characteristic biconvex needle-shaped clefts left by the dissolved crystals of cholesterol within the occluded vessels in the lower dermis, with no evidence of vasculitis. Warfarin and atenolol were discontinued, atorvastatin was administered and supportive measures were provided. The skin lesions improved; however, the patient required dialytic treatment. Twelve months later he became asymptomatic and did not need further dialysis.

*Case 2.* An 80-year-old man was admitted to our hospital because of fever and malaise 48 h before admission. Pain in the right fifth toe had been present during the previous week and livedo reticularis on lower limbs for 2 months prior to admission. He had a long smoking history and presented chronic obstructive pulmonary disease, hypertension, ischaemic cardiomyopathy, hypercholesterolaemia and chronic renal failure (plasma creatinine 194  $\mu\text{mol/l}$ ). Treatment with

enoxaparin 40 mg/day for 10 days had been given 3 months prior to his admission.

Examination revealed a temperature of 38.7°C, a blood pressure of 150/90 mmHg and an aortic systolic murmur. He had bilateral livedo reticularis on his lower limbs and lower trunk with necrosis of right fifth toe; peripheral pulses and temperature were normal (Fig. 1).

Laboratory examination revealed a total white cell count of  $11.8 \times 10^9/\text{l}$  with 83% neutrophils but no eosinophilia, plasma urea 42.1 mmol/l, plasma creatinine 423  $\mu\text{mol/l}$ , total protein 56 g/l (normal 60–80), albumin 26 g/l (normal 35–50), triglycerides 2.4 g/l (normal 0.4–1.6) and ESR 113 mm/h. Urine analysis: urinary protein excretion 1.17 g/24 h (normal <150 mg/24 h), and 2+ for red blood cells. A test for antinuclear antibodies was positive at a titre of 1:320 with a speckled pattern and lupus anticoagulant was positive at a titre of 35.8 with ratio 1.29. A thoracic and abdominal CT scan showed a massive thrombosis of abdominal aorta and splenic ischaemic lesions. Lesional skin biopsy was performed and treatment with prednisolone and cyclophosphamide was started as a result of a presumptive panarteritis nodosa diagnosis. The biopsy showed needle-shaped clefts left by dissolved crystals of cholesterol in the vessels (Fig. 2). For that reason, previous medications were discontinued; however, the patient died 28 days after admission because of several complications (cardiac failure, cerebral infarction and abdominal pain). Autopsy could not be performed.

### DISCUSSION

CES is a complication of atherosclerotic vascular disease that results from cholesterol crystals embolization. These originate in atheromatous plaques in major arteries and go to many organs including skin, kidneys, gastrointestinal and central nervous system. The cholesterol crystals occlude small and peripheral arteries causing local ischaemia and organ damage. This entity



Fig. 1. (a) Livedo reticularis on limbs with central ischaemic lesion. (b) Cyanotic ischaemic lesions with necrosis of fifth toe.

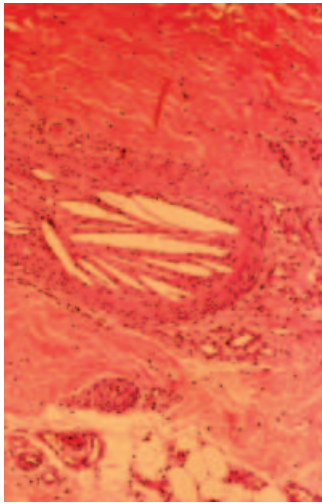


Fig. 2. Cholesterol crystals causing luminal occlusion and intimal hyperplasia. An arteriole is occluded by needle-shaped clefts (haematoxylin and eosin, original  $\times 200$ ).

typically affects patients over 60 years of age who have two or more risk factors for atherosclerotic vascular disease (1, 2). Although the syndrome can occur spontaneously (4), it is often possible to identify one or more precipitating factors, e.g. vascular procedures (3), cardiac or aorta surgery (5), treatment with anticoagulants (2, 3, 6) or thrombolytic agents (3, 7). Both patients described above had several risk factors for atherosclerosis and they had received anticoagulants for some months prior to diagnosis. The latent period until appearance of clinical findings can vary from days to months (3), as in our second case.

Diagnosis of CES requires a high level of clinical suspicion. Clinical manifestations can be varied (1). Both patients showed the classical triad of hypertension, acute renal failure and typical skin lesions. Skin lesions are observed in between 35 and 100% of patients and are probably the first signs of the disease. Cutaneous manifestations are varied including a symmetrical livedo reticularis, acrocyanosis, ulcerations, purpura, severe leg and/or foot pain and focal digital ischaemia (the purple-toe syndrome) (1–3, 8). The cutaneous lesions are usually painful and peripheral pulses are normal. These lesions can mimic other systemic diseases like vasculitis, which is an important differential diagnosis (9). An increase in ESR, eosinophilia, transient elevation of muscle enzymes, thrombopenia and hypocomplementaemia are commonly associated but not always present (3). Eosinophilia was present in case 1 and ESR was increased in both cases.

Skin biopsy of affected tissue is diagnostic in 92% of the cases (1, 3). Biopsy must include an area between middle to deep dermis. The characteristic needle-shaped spaces left by the dissolved crystals within the lumen of arterioles from affected skin were observed in our patients.

The syndrome is associated with a high mortality rate, reaching 80% (1, 2). The prognosis depends on the degree of organ affection and the severity of the underlying vascular disease, as seen from the fatal outcome in case 2. There is no current effective therapy (10). Some researchers have suggested treatments like iloprost (a prostacyclin analogue) (11), simvastatin (12) or corticosteroids (13) but none of them have been shown to have a clear beneficial effect. Conventional treatment is through supportive measures that include blood pressure control, renal replacement therapy whenever necessary and withdrawal of anticoagulants except in cases with high risk of embolism.

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